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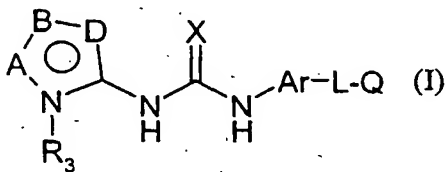
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WO 02/066442 A1

(54) Title: PROCESS FOR SYNTHESIS OF HETEROARYL-SUBSTITUTED UREA COMPOUNDS USEFUL AS ANTI-INFLAMMATORY AGENTS



(57) Abstract: This invention relates to novel processes for preparing heteroaryl-substituted urea compounds of formula (I) which are useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease.

**Process for Synthesis of Heteroaryl-substituted Urea Compounds Useful as
Antiinflammatory Agents**

RELATED APPLICATION DATA

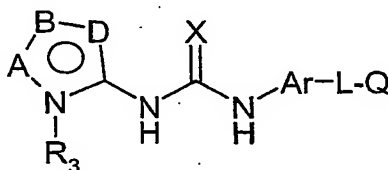
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This application claims benefit to US provisional application number 60/268,841 filed February 15, 2001.

TECHNICAL FIELD OF THE INVENTION

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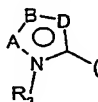
This invention relates to novel processes for preparing heteroaryl-substituted urea compounds of formula (I):



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(I)

which are useful for treating diseases and pathological conditions involving inflammation such as chronic inflammatory disease. X, Ar, L, Q and

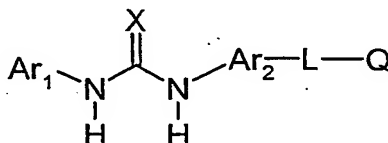


are described hereinbelow.

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BACKGROUND OF THE INVENTION

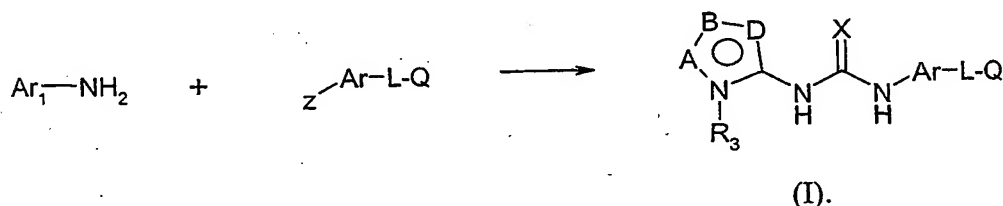
Aryl- and heteroaryl-substituted ureas have been described as inhibitors of cytokine production and effective therapeutics in cytokine-mediated diseases including inflammatory and autoimmune diseases. Examples of such compounds are reported in U.S. 6,080,763, WO 00/43384 and WO 00/55139 including aryl- or heteroaryl-substituted ureas of the formula shown below:



Among the favored Ar_1 are substituted or unsubstituted aryl or heteroaryl groups, including those defined below in this application.

A preferred step in the synthesis of this class of compounds is the formation of a urea bond as illustrated in Scheme I.

Scheme I

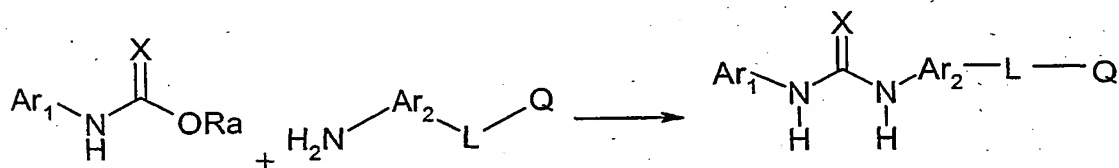


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In Scheme I, Z can be an isocyanate or isothiocyanate or an amine (in which case the isocyanate or isothiocyanate is formed *in situ*) or Z can be $R_bOC(O)NH$ where OR_b is a leaving group. The reaction may also be carried out in the reverse sense (i.e., $Ar_1-Z + H_2N-Ar-L-Q$).

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US application 09/611,109 discloses a method of making similar compounds by reacting a carbamate, made from reaction of a Ar_1-NH_2 and a haloformate, and the appropriate the amine as shown below to form the product compound:

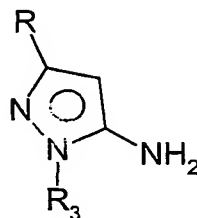


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The methods previously described for the synthesis of (I) require the preparation of intermediate (II), where Ar_1 is the desired aryl or heteroaryl group. Preparation of (II) often requires a multi-step synthesis. For example the preferred intermediate (IIa) shown below is prepared by reaction of an aryl hydrazine with a ketonitrile. See also US application serial nos. 09/698,442 and 09/735,160, and US provisional serial no. 60/216,283. Often, preferred aryl hydrazines and ketonitriles are not available commercially and must themselves be synthesized. This non-convergent approach

also makes it inconvenient and tedious to prepare a series of analogs of formula (I)

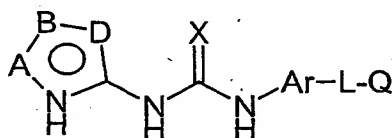
differing only in R₃:



IIa

- 5 Recent reports in the chemical literature described improved methods for the coupling of aryl groups to NH-containing heterocycles. For example, P.Y.S. Lam et al. (Tetrahedron Letters, 1998, 2941) describes the coupling of aryl groups to NH-containing heterocycles in the presence of cupric acetate and base. The reaction occurs under mild conditions and is not air-sensitive. The reaction is successful with
- 10 a variety of aryl boronic acids, many of which are commercially available.

In the novel process disclosed herein, R₃ is coupled to intermediate (Ia) in a final step.

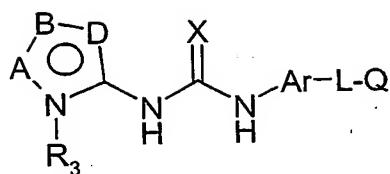


(Ia)

15 Intermediates required for the final coupling step of R₃ to Ia are often commercially available or readily prepared.

20 BRIEF SUMMARY OF THE INVENTION

It is therefore an object of this invention to provide a process for the preparation of the aryl- and heteroaryl-substituted urea compounds of the formula (I) shown below:

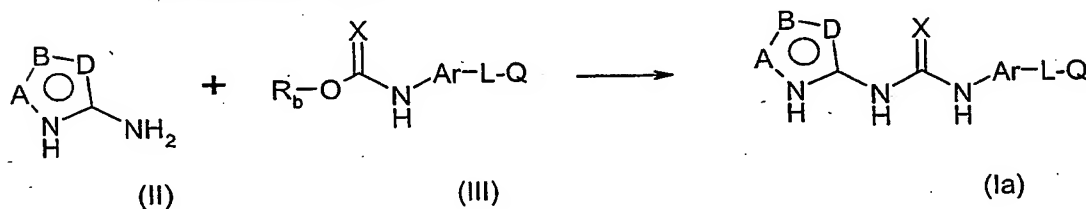


(I)

comprising the steps of:

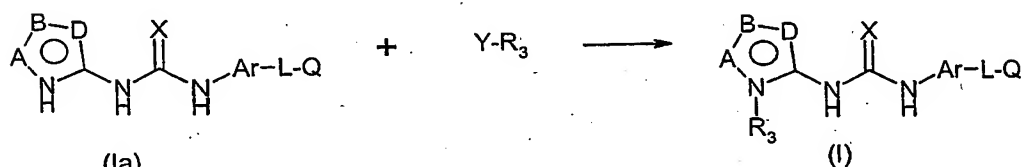
- 1) reacting an intermediate compound of the formula (III) with a heteroarylamine compound of the formula (II), to form an intermediate compound of the formula (Ia). Suitable conditions and the definitions for X, Ar, L, Q and

are described hereinbelow:



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- 2) coupling the product of step 1), formula (Ia), with an electrophile Y-R₃, to form a compound of the formula (I). Suitable conditions and the definitions of Y and R₃ are described hereinbelow:

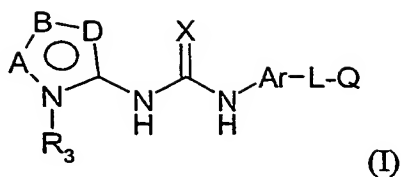


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DETAILED DESCRIPTION OF THE INVENTION

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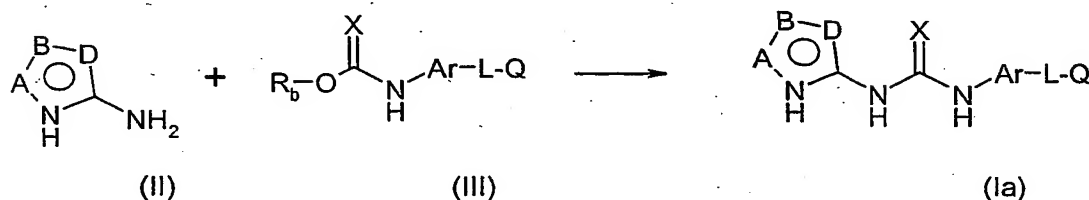
The present invention is directed to the synthesis of compounds having the formula (I):



said process comprising:

- 1) reacting an intermediate compound of the formula (III) with a heteroarylamine compound of the formula (II), said reaction occurring in the presence of a suitable base such as triethylamine, diisopropylethylamine, N-methylpyrrolidine, DBU, DMAP, N-methylmorpholine, pyridine or methyl pyridine, preferably diisopropylethylamine;

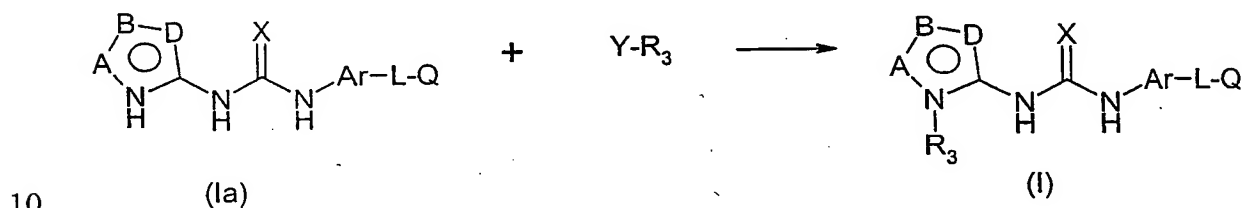
and in a suitable organic solvent, preferably a polar non-protic organic solvent selected from NMP, acetonitrile, DMF, DMAC and DMSO, preferably DMSO; and at a suitable temperature of about 40-100°C, preferably about 80°C for a reaction time of about 1 to 20 hours, preferably 4-10 hours, to form an intermediate compound of the formula (Ia):



- wherein R_b represents a group that renders R_b-O- a leaving group, for example aryl such as phenyl or a C_{2-3} halocarbon, such as 2,2,2-trichloroethyl, preferably R_b is 2,2,2-trichloroethyl. Certain (II) are either available or can be obtained by known methods, reference in this regard may be made to US application serial nos. 09/505,582, 09/484,638, 09/698,442 and 09/735,160, and US provisional serial no. 60/216,283, each incorporated herein by reference in their entirety.

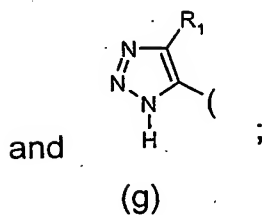
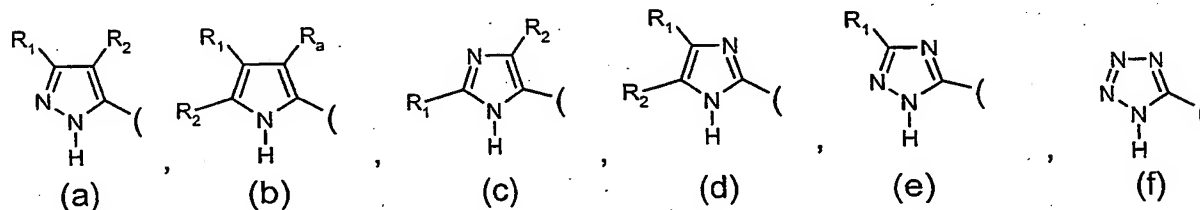
- 2) coupling the product of step 1), formula (Ia), with electrophile $Y-R_3$, preferably present in about a two-fold molar excess, wherein the moiety Y is a group selected from BR_2 , BR_3M , SiR_3 and SnR_3 wherein R is C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or halogen (the halogen is preferably fluorine) and wherein M is Na, Li or K, preferably

Y is B(OH)₂, said coupling reaction occurring in the presence of a suitable base such as triethylamine or pyridine, preferably pyridine, preferably present in about a two-fold molar excess, and in the presence of a suitable catalyst such as Cu(OAc)₂, [Cu(OH).TMEDA]₂Cl₂ or CuCO₃.Cu(OH)₂, preferably Cu(OAc)₂, preferably present at about a 1.5 molar excess; and said coupling reaction occurring at a suitable temperature of about 20-30°C, in a suitable solvent such as methylene chloride, 1,4-dioxane, N-methylpyrrolidinone, THF and DMF, preferably, methylene chloride, to form a compound of the formula (I):



15 the heteroaryl ring in formulas (I), (Ia) and (II):

; is chosen from:



20 wherein for the above heteroaryl rings (a), (b) and (d), R₁ and R₂ or R_a can join to form a benzo ring fused to the heterocyclic ring to form a bicyclic heteroaryl;

Ar is:

phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, benzofuran, indanyl, indenyl or indole each being optionally substituted with one to three R₂ groups;

L, a linking group, is:

- 5 a bond or a C₁₋₁₀ saturated or unsaturated branched or unbranched carbon chain, wherein one or more C atoms are optionally replaced by O, N, or S(O)_m; and wherein L is optionally partially or fully halogenated and optionally independently substituted with one to two oxo groups, nitrile, phenyl or one or more C₁₋₄ alkyl optionally substituted by one or more halogen atoms;
- 10 or L is a cyclic group which is:
- a) a C₅₋₈ cycloalkyl or cycloalkenyl optionally substituted with 1-2 oxo groups, 1-3 C₁₋₄ branched or unbranched alkyl or C₁₋₄ alkoxy;
- b) phenyl, furan, thiophene, pyridine, pyrimidine, pyridinone, dihydropyridinone, maleimide, dihydromaleimide or pyrazine each being optionally independently
- 15 substituted with 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄alkoxy, cyano, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, or halogen;
- wherein said cyclic group is optionally attached to a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q, said carbon chain is optionally partially or fully halogenated
- 20 and wherein one or more methylene groups are optionally replaced by O, N, S(O)_m, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;
- Methods for making 'L' are known in the art, and are also to be found in U.S.
- 25 Patent Application Nos. 09/484,638 and 09/714,539.

Q is selected from the group consisting of:

- a) phenyl, naphthyl, pyridine, pyrimidine, pyridazine, furan, thiophene, pyran,
- 30 naphthyridine and oxazo[4,5-*b*]pyridine which are optionally substituted with one to three groups selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino and C₁₋₆ alkyl-S(O)_m;
- b) tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, *N*-morpholine, *N*-thiomorpholine, *N*-thiomorpholine sulfoxide, *N*-thiomorpholine

sulfone, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone which are optionally substituted with one to three groups selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, and C₁₋₃ alkoxy-C₁₋₃ alkyl;

- 5 c) C₁₋₆ alkoxy, tertiary amine wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C₁₋₃ alkyl and C₁₋₅ alkoxyalkyl and phenyl wherein the phenyl ring is optionally substituted with one to two groups selected from the group consisting of halogen, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m and phenyl-S(O)_m, wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C₁₋₆ alkoxy, or di-(C₁₋₃ alkyl)amino;
- 10

R₁ is selected from the group consisting of:

15

- (a) C₃₋₁₀ branched or unbranched alkyl, which may optionally be partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, C₃₋₈ cycloalkyl, C₅₋₈ cycloalkenyl, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated and di(C₁₋₃)alkylaminocarbonyl;
- 20
- (b) C₃₋₇ cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which are optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from O, S, >C=O and >C=S;
- 25
- 30 (c) C₃₋₁₀ branched alkenyl optionally partially or fully halogenated, and optionally substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl,

- pyridazinyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated and di(C₁₋₃)alkylaminocarbonyl;
- (d) C₅₋₇ cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;
- (e) cyano; and,
- (f) methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

R₂ is selected from the group consisting of:

a C₁₋₆ branched or unbranched alkyl optionally partially or fully halogenated, acetyl, aroyl, C₁₋₄ branched or unbranched alkoxy optionally partially or fully halogenated, halogen and methoxycarbonyl;

R₃ is selected from the group consisting of:

- a) a phenyl, naphthyl or heteroaryl group selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, tetrahydrofuryl, isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzofuranyl, benzoxazolyl, benzisoxazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl, naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl wherein such phenyl, naphthyl or heteroaryl group is optionally substituted with one to five groups selected from the group consisting of a C₁₋₆ branched or unbranched alkyl, phenyl, naphthyl, heteroaryl group selected from the groups hereinabove described, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halo, cyano, C₁₋₃ alkyloxy which may

- optionally be partially or fully halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety is selected from the group hereinabove described, nitro, di-(C₁₋₃)alkylamino, di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, , di-(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅ alkyl, R₅-C₁₋₅ alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅ alkyl-N(R₈)-; and
- 5 b) a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and benzocycloheptenyl, or a fused heterocyclyl selected from cyclopentenopyridine, cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanthiophene and cyclohexanthiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl, heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocycliloxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, di-(C₁₋₃)alkylamino, di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ branched or unbranched alkyl, di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₉-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkoxy, R₁₁-C(O)-C₁₋₅ alkyl and R₁₂-C₁₋₅ alkyl-N(R₁₃)-;
- 10 20 25

R₁ and R₂ taken together optionally form a fused phenyl or pyridinyl ring;

each R₈ or R₁₃ is independently C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated;

30

each R₄, R₅, R₆, R₇, R₉, R₁₀, R₁₁ and R₁₂ is independently selected from the group consisting of:

N-morpholine and piperazine;

R_a equals the definitions of R_1 , wherein R_a and R_1 can be simultaneously the same or different;

each m is independently 0, 1 or 2;

5

X is O or S;

and if Ar, L, Q or R_1 through R_{13} contains group, such as NH, NH_2 or OH, that could react during the urea formation (step 1) or coupling step (step 2) one may employ protection and deprotection chemistry known in the art to mask these groups during these steps.

10

Particular work-up and purification methods depending on the compound desired will be apparent to those of ordinary skill in the art. A preferred method is shown in Example 1 in the present specification.

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A preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula(I) wherein Ar is naphthyl, tetrahydronaphthyl, indanyl or indenyl.

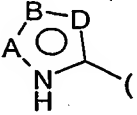
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A more preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula(I) wherein Ar is naphthyl.

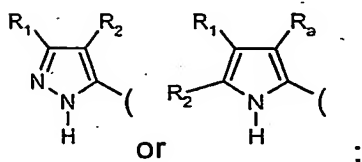
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A yet more preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula (I), as described in the immediate previous paragraph, wherein:

the heteroaryl ring



is:



Ar is 1-naphthyl;

L is C₁₋₆ saturated or unsaturated branched or unbranched carbon chain

wherein

5 one or more C atoms are optionally replaced by O, N or S(O)_m; and wherein said linking group is optionally substituted with one to two oxo groups, C₁₋₄ alkyl optionally substituted by one or more halogen atoms;

or L is cyclopentenyl, cyclohexenyl, cycloheptenyl, each optionally substituted with an oxo group or 1-3 C₁₋₄ branched or unbranched alkyl or C₁₋₄alkoxy;

10 or L is phenyl, pyridine, furan or thiophene each being optionally independently substituted with 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄alkoxy, cyano, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m or halogen;

wherein said cyclic group is optionally attached to a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q, said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, N or S(O)_m, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

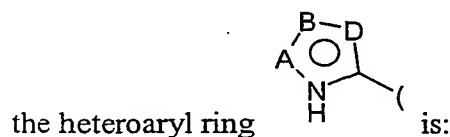
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R₁ is C₃₋₄alkyl branched or unbranched, cyclopropyl or cyclohexanyl optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups;

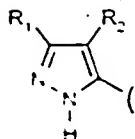
R₃ is selected from the group consisting of

25 phenyl, pyridinyl each being optionally substituted with one to five groups selected from the group consisting of a C₁₋₆ branched or unbranched alkyl, phenyl, naphthyl, pyridinyl, C₁₋₆ branched or unbranched alkyl, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halo, cyano, C₁₋₃ alkyloxy
30 which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy, pyridinyloxy, nitro, di-(C₁₋₃)alkylamino, di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, di-(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅alkyl, R₅-C₁₋₅alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅ alkyl-N(R₈)-

A yet further preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula (I), as described in the immediate previous paragraph, wherein

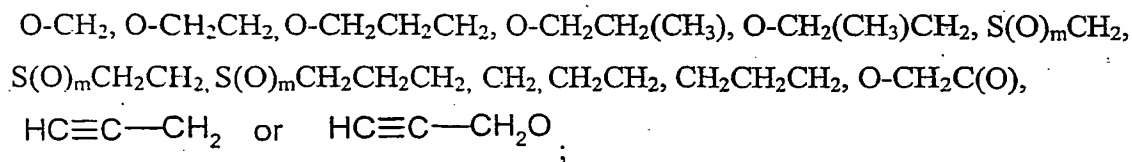


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A still yet further preferred subgeneric aspect of the invention comprises a process of producing compounds of the formula (I), as described in the immediate previous paragraph, wherein L is C₁₋₅ saturated carbon chain wherein one or more C atoms are optionally independently replaced by O, N or S(O)_m; and wherein said linking group is optionally substituted with 0-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

More particularly preferred embodiments of the process of the invention is where L is L is:



and Q is *N*-morpholino.

A even more particularly preferred embodiment of L is O-CH₂CH₂.

The compounds produced by the novel process of the invention may be prepared as physiologically and pharmaceutically acceptable salts, as may seem appropriate to one of ordinary skill in the art.

The compounds produced by the novel process of the invention are only those which are contemplated to be 'chemically stable' as will be appreciated by those skilled in the art. For example, a compound which would have a 'dangling valency', or a 'carbanion' are not compounds contemplated to be made by the novel process.

5

All terms as used herein in this specification, unless otherwise stated, shall be understood in their ordinary meaning as known in the art. For example, "C₁₋₄alkoxy" is a C₁₋₄alkyl with a terminal oxygen, such as methoxy, ethoxy, propoxy, pentoxy and hexoxy. All alkyl, alkenyl and alkynyl groups shall be understood as being branched or unbranched where structurally possible and unless otherwise specified. Other more specific definitions are as follows:

10

The term "aroyl" as used in the present specification shall be understood to mean "benzoyl" or "naphthoyl".

15

OMe : methoxy;

NMP: 1-methyl-2-pyrrolidinone;

THF: tetrahydrofuran;

DMF: N,N'-dimethylformamide;

20

DMAC: N,N'-dimethylacetamide;

DMSO: dimethylsulfoxide;

DMAP: 4-dimethylaminopyridine;

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene;

EtOAc: ethyl acetate

25

EtOH: ethanol

TMEDA: N, N, N', N'-tetramethylethylenediamine

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating preferred embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

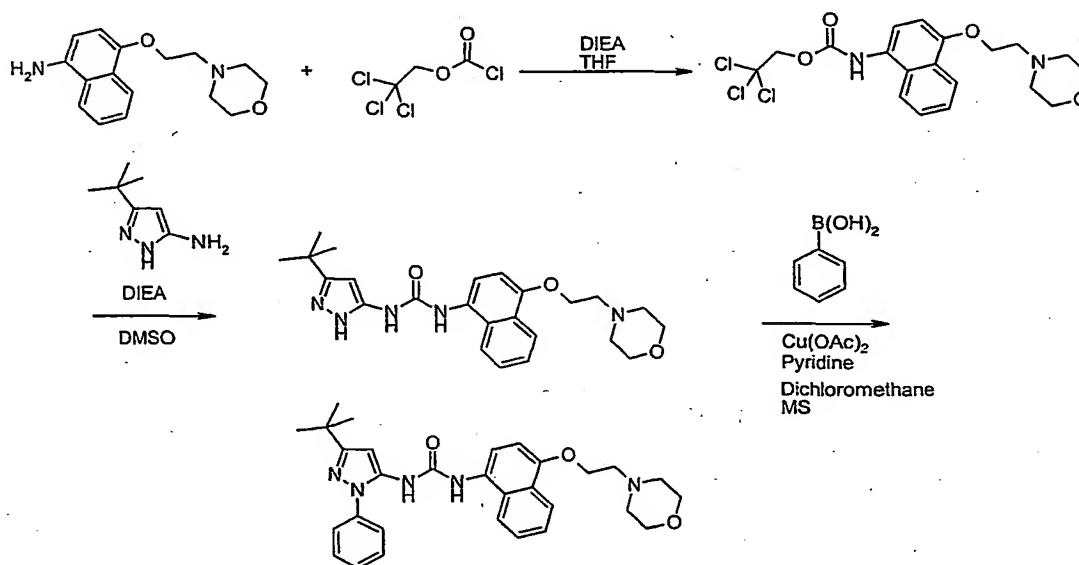
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SYNTHETIC EXAMPLES

5

Example 1

Synthesis of 1-(5-tert-Butyl-2-phenyl-2H-pyrazol-3-yl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea:



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To a solution of 4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-ylamine (10.9 g, 40 mmol) and N, N-diisopropylethylamine (10 mL) in THF (80 mL), cooled to -10°C under argon, was added 2,2,2-trichloroethyl chloroformate (5.6 mL, 40 mmol) via syringe over 10 min. Upon stirring at -10°C for 40 min, EtOAc (100 mL) and water (100 mL) were added. The organic layer was washed with brine, dried (MgSO_4), filtered and concentrated in vacuo. The crude product was triturated (ether), filtered, washed (ether) and air-dried to give a first crop as a slightly pink white solid (11.1 g). The filtrate was concentrated in vacuo, triturated (ether), filtered, washed (ether) and dried, providing a second crop of 4.6 g. A total of 15.7 g (88%) of [4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-carbamic acid 2,2,2-trichloroethyl ester, was obtained as a pink solid, m.p. $124-125^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 2.66(t, 4H), 2.97(t, 2H), 3.75(t,

4H), 4.31(t, 3H), 4.88(s, 2H), 6.80(d, 1H), 6.94(s, 1H), 7.58(m, 3H), 7.87(d, 1H), 8.29(d, 1H); MS (CI) 447(M⁺ +H).

5 A solution of the above trichloroethyl carbamate (4.5 g, 10 mmol), (5-tert-butyl-2-aminopyrazole 1.4 g, 10 mmol), and N, N-diisopropylethylamine (1.8 mL, 10 mmol) in DMSO (100 mL) was heated at 80 °C for 14 h. The mixture was cooled to room temperature, EtOAc (100 mL) and water (100 mL) were added. The organic layer was washed with brine, dried (MgSO₄), filtered, concentrated in vacuo, triturated (ether), washed (hexane) and dried in air to give 1-(5-tert-butyl-2H-pyrazol-3-yl)-3-
10 [4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea as a pale pink solid (3.7g, 84%), mp 206-207 °C, ¹H NMR (DMSO) δ 1.25(s, 9H), 2.53(t, 4H), 2.83(t, 2H), 3.58(t, 4H), 4.25(t, 2H), 5.87(s, 1H), 6.96(d, 1H), 7.56(m, 2H), 7.82(d, 1H), 8.03(d, 1H), 8.18(d, 1H), 9.17(s, 1H), 12.06(s, 1H); MS (CI) 438(M⁺ +H).

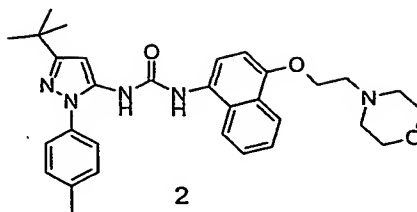
15 A mixture of the above urea (0.022 g, 0.050 mmol), phenylboronic acid (0.012 g, 0.1 mmol), copper (II) acetate (0.014 g, 0.075 mmol), pyridine (0.01 mL, 0.1 mmol) and molecular sieves (4Å activated, 0.030 g) in methylene chloride (2 mL) was stirred at room temperature for 14 h under air. After filtration through diatomaceous earth, the filtrate was concentrated in vacuo and purified by flash chromatography (EtOAc
20 100% to EtOH 100%) to give the title compound as a yellow-white solid (0.02 g, 73%), mp 142-143°C; ¹H NMR (DMSO) δ 1.26(s, 9H), 2.53(t, 4H) 2.83(t, 2H), 3.57(t, 4H), 4.24(t, 2H), 6.34(s, 1H), 6.94(d, 1H), 7.40(d, 1H), 7.55(m, 7H), 7.90(d, 1H), 8.15(d, 1H), 8.82(s, 1H), 8.92(s, 1H); MS (CI) 514(M⁺ +H).

25

Example 2

Synthesis of 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea:

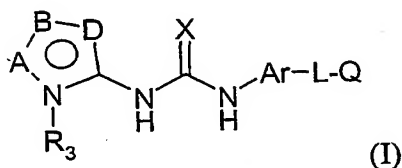
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The title compound was prepared as described in the final step of Example 1 from 1-(5-tert-butyl-2H-pyrazol-3-yl)-3-[4-(2-morpholin-4-yl-ethoxy)-naphthalen-1-yl]-urea (0.022 g, 0.050 mmol), and p-tolylboronic acid (0.014 g, 0.1 mmol), using copper (II) acetate (0.014 g, 0.075 mmol), pyridine (0.01 mL, 0.1 mmol), molecular sieves (4Å activated, 0.030 g) and methylene chloride (2 mL). The title compound was obtained as a yellow-white solid (0.013 g, 50%), mp 144 –146 °C; ¹H NMR (DMSO) δ 1.26(s, 9H), 2.36(s, 3H), 2.53(t, 4H) 2.82(t, 2H), 3.52(t, 4H), 4.23(t, 2H), 6.32(s, 1H), 6.94(d, 1H), 7.33(d, 1H), 7.42(d, 1H), 7.54(m, 3H), 7.90(d, 1H), 8.15(d, 1H), 8.18(d, 1H), 8.82(s, 1H), 8.96(s, 1H); MS (CI) 528(M⁺ +H).

What is claimed is:

1. A process of making a compound of the formula (I):

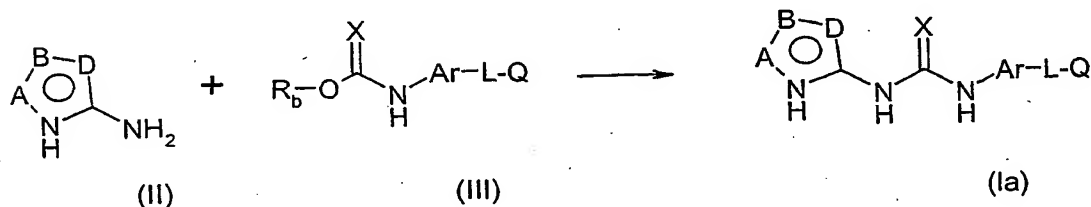


said process comprising:

10

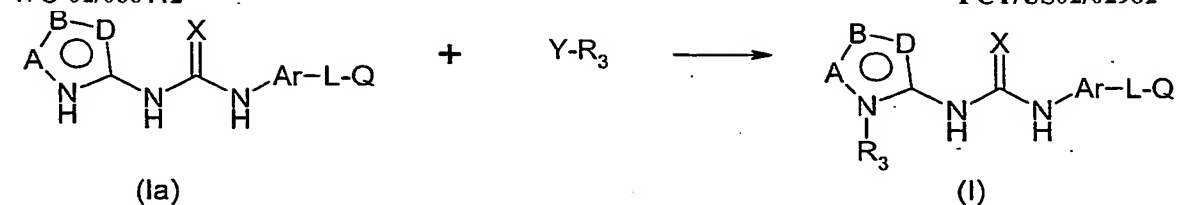
- 1) reacting an intermediate compound of the formula (III) with a heteroarylamine compound of the formula (II), said reaction occurring in the presence of a suitable base, in a polar non-protic organic solvent and at a suitable temperature of about 40-100°C for a reaction time of about 1 to 20 hours, to form an intermediate compound of the formula (Ia):

15



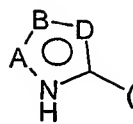
- 20 wherein R_b represents phenyl or a C_{2-3} halocarbon;

- 2) coupling the product of step 1), formula (Ia), with electrophile $Y-R_3$, wherein the moiety Y is a group selected from BR_2 , BR_3M , SiR_3 and SnR_3 wherein R is C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or halogen and wherein M is Na, Li or K, said
- 25 coupling reaction occurring in a suitable base, and in the presence of a suitable catalyst; and said coupling reaction occurring at a suitable temperature of about 20-30°C, in a suitable solvent, to form a compound of the formula (I):

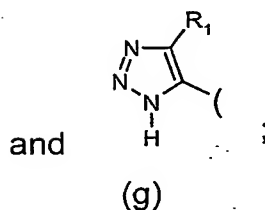
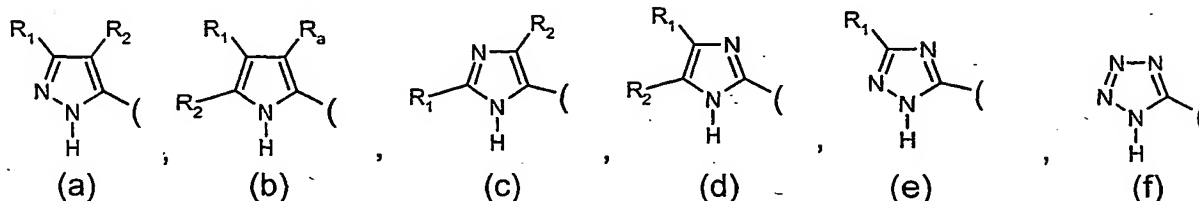


wherein:

the heteroaryl ring in formulas (I), (Ia) and (II):



; is chosen from:



wherein for the above heteroaryl rings (a), (b) and (d), R_1 and R_2 or R_a can join to form a benzo ring fused to the heterocyclic ring to form a bicyclic heteroaryl;

Ar is:

phenyl, naphthyl, quinoline, isoquinoline, tetrahydronaphthyl, benzofuran, indanyl, indenyl or indole each being optionally substituted with one to three R_2 groups;

L, a linking group, is:

a bond or a C_{1-10} saturated or unsaturated branched or unbranched carbon chain, wherein one or more C atoms are optionally replaced by O, N, or $S(O)_m$; and wherein L is optionally partially or fully halogenated and optionally independently substituted

with one to two oxo groups, nitrile, phenyl or one or more C₁₋₄ alkyl optionally

substituted by one or more halogen atoms;

or L is a cyclic group which is:

- a) a C₅₋₈ cycloalkyl or cycloalkenyl optionally substituted with 1-2 oxo groups, 1-3 C₁₋₄ branched or unbranched alkyl or C₁₋₄ alkoxy;
- b) phenyl, furan, thiophene, pyridine, pyrimidine, pyridinone, dihydropyridinone, maleimide, dihydromaleimide or pyrazine each being optionally independently substituted with 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄alkoxy, cyano, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m, or halogen;
- wherein said cyclic group is optionally attached to a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q, said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, N, S(O)_m, wherein said methylene groups are further optionally independently substituted with 1-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

Q is selected from the group consisting of:

- phenyl, naphthyl, pyridine, pyrimidine, pyridazine, furan, thiophene, pyran, naphthyridine and oxazo[4,5-*b*]pyridine which are optionally substituted with one to three groups selected from the group consisting of halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino and C₁₋₆ alkyl-S(O)_m;
- tetrahydropyran, tetrahydrofuran, 1,3-dioxolanone, 1,3-dioxanone, 1,4-dioxane, *N*-morpholine, *N*-thiomorpholine, *N*-thiomorpholine sulfoxide, *N*-thiomorpholine sulfone, cyclohexanone, cyclohexanol, pentamethylene sulfide, pentamethylene sulfoxide, pentamethylene sulfone, tetramethylene sulfide, tetramethylene sulfoxide and tetramethylene sulfone which are optionally substituted with one to three groups selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino-C₁₋₃ alkyl, and C₁₋₃ alkoxy-C₁₋₃ alkyl;

C₁₋₆ alkoxy, tertiary amine, wherein the amino nitrogen is covalently bonded to groups selected from the group consisting of C₁₋₃ alkyl and C₁₋₅ alkoxyalkyl and phenyl wherein the phenyl ring is optionally substituted with one to two groups selected from

the group consisting of halogen, C₁₋₆ alkoxy, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m and phenyl-S(O)_m, wherein the phenyl ring is optionally substituted with one to two groups consisting of halogen, C₁₋₆ alkoxy, or di-(C₁₋₃ alkyl)amino;

5 R₁ is selected from the group consisting of:

C₃₋₁₀ branched or unbranched alkyl, which may optionally be partially or fully halogenated, and optionally substituted with one to three phenyl, naphthyl or heterocyclic groups selected from the group consisting of pyridinyl, pyrimidinyl, 10 pyrazinyl, pyridazinyl, thienyl, furyl, isoxazolyl and isothiazolyl; each such phenyl, naphthyl or heterocycle selected from the group hereinabove described, being substituted with 0 to 5 groups selected from the group consisting of halogen, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, C₃₋₈ cycloalkyl, C₅₋₈ cycloalkenyl, cyano, C₁₋₃ alkyloxy which is optionally partially or 15 fully halogenated and di(C₁₋₃)alkylaminocarbonyl;

C₃₋₇ cycloalkyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl and bicycloheptanyl, which are optionally partially or fully halogenated and optionally 20 substituted with one to three C₁₋₃ alkyl groups, or an analog of such cycloalkyl group wherein one to three ring methylene groups are replaced by groups independently selected from O, S, >C=O and >C=S;

C₃₋₁₀ branched alkenyl optionally partially or fully halogenated, and optionally 25 substituted with one to three C₁₋₅ branched or unbranched alkyl, phenyl, naphthyl or heterocyclic groups, with each such heterocyclic group being independently selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, isoxazolyl and isothiazolyl, and each such phenyl, naphthyl or heterocyclic group being substituted with 0 to 5 groups selected from halogen, C₁₋₆ branched or 30 unbranched alkyl which is optionally partially or fully halogenated, cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated and di(C₁₋₃)alkylaminocarbonyl;

C₅₋₇ cycloalkenyl selected from the group consisting of cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, bicyclohexenyl and bicycloheptenyl, wherein such cycloalkenyl group is optionally substituted with one to three C₁₋₃ alkyl groups;

- 5 cyano; and,
methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl;

R₂ is selected from the group consisting of:

- a C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated, acetyl,
10 aroyl, C₁₋₄ branched or unbranched alkoxy optionally partially or fully halogenated,
halogen and methoxycarbonyl;

R₃ is selected from the group consisting of:

- a phenyl, naphthyl or heteroaryl group selected from the group consisting of
15 pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, tetrahydrofuryl,
isoxazolyl, isothiazolyl, quinolinyl, isoquinolinyl, indolyl, benzofuranyl,
benzoxazolyl, benzisoxazolyl, benzothiofuranyl, cinnolinyl, pterindinyl, phthalazinyl,
naphthypyridinyl, quinoxalinyl, quinazolinyl, purinyl and indazolyl wherein such
phenyl, naphthyl or heteroaryl group is optionally substituted with one to five groups
20 selected from the group consisting of a C₁₋₆ branched or unbranched alkyl, phenyl,
naphthyl, heteroaryl group selected from the groups hereinabove described, C₁₋₆
branched or unbranched alkyl which is optionally partially or fully halogenated,
cyclopropyl, cyclobutyl, cyclopentanyl, cyclohexanyl, cycloheptanyl,
bicyclopentanyl, bicyclohexanyl, bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅
25 alkyl, halo, cyano, C₁₋₃ alkyloxy which may optionally be partially or fully
halogenated, phenyloxy, naphthyloxy, heteraryloxy wherein the heterocyclic moiety
is selected from the group hereinabove described, nitro, di-(C₁₋₃)alkylamino, di-(C₁₋₃)
alkyl aminocarbonyl, C₁₋₅ alkyl-C(O)-C₁₋₄ alkyl, di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, , di-
(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅ alkyl, R₅-C₁₋₅ alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅
30 alkyl-N(R₈)-; and

a fused aryl selected from the group consisting of benzocyclobutanyl, indanyl,
indenyl, dihydronaphthyl, tetrahydronaphthyl, benzocycloheptanyl and
benzocycloheptenyl, or a fused heterocyclyl selected from cyclopentenopyridine,

- cyclohexanopyridine, cyclopentanopyrimidine, cyclohexanopyrimidine, cyclopentanopyrazine, cyclohexanopyrazine, cyclopentanopyridazine, cyclohexanopyridazine, cyclopentanoquinoline, cyclohexanoquinoline, cyclopentanoisoquinoline, cyclohexanoisoquinoline, cyclopentanoindole, cyclohexanoindole, cyclopentanobenzoxazole, cyclohexanobenzoxazole, cyclopentanthiophene and cyclohexanthiophene; wherein the fused aryl or fused heterocyclyl ring is substituted with 0 to 3 groups independently selected from phenyl, naphthyl, heterocyclyl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thienyl, furyl, isoxazolyl, and isothiazolyl, C₁₋₆ branched or unbranched alkyl which is optionally partially or fully halogenated, halo, cyano, C₁₋₃ alkyloxy which is optionally partially or fully halogenated, phenyloxy, naphthyloxy, heterocyclyloxy wherein the heterocyclyl moiety is selected from the group hereinabove described, nitro, di-(C₁₋₃)alkylamino, di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₄ alkyl-OC(O), C₁₋₅ alkyl-C(O)-C₁₋₄ branched or unbranched alkyl, di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, R₉-C₁₋₅ alkyl, R₁₀-C₁₋₅ alkoxy, R₁₁-C(O)-C₁₋₅ alkyl and R₁₂-C₁₋₅ alkyl-N(R₁₃)-;

R₁ and R₂ taken together optionally form a fused phenyl or pyridinyl ring;

- each R₈ or R₁₃ is independently C₁₋₄ branched or unbranched alkyl optionally partially or fully halogenated;

each R₄, R₅, R₆, R₇, R₉, R₁₀, R₁₁ and R₁₂ is independently selected from the group consisting of:

- N*-morpholine and piperazine;

R_a equals the definitions of R₁, wherein R_a and R₁ can be simultaneously the same or different;

- each *m* is independently 0, 1 or 2;

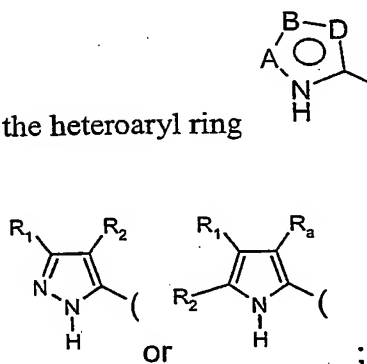
X is O or S.

2. The process according to claim 1 wherein Ar is naphthyl, tetrahydronaphthyl, indanyl or indenyl.

3. The process according to claim 2 wherein Ar is naphthyl.

4. The process according to claim 3 wherein

the heteroaryl ring is:



Ar is 1-naphthyl;

L is C₁₋₆ saturated or unsaturated branched or unbranched carbon chain wherein

one or more C atoms are optionally replaced by O, N or S(O)_m; and wherein said linking group is optionally substituted with one to two oxo groups, C₁₋₄ alkyl optionally substituted by one or more halogen atoms;

or L is cyclopentenyl, cyclohexenyl, cycloheptenyl, each optionally substituted with an oxo group or 1-3 C₁₋₄ branched or unbranched alkyl or C₁₋₄alkoxy;

or L is phenyl, pyridine, furan or thiophene each being optionally independently substituted with 1-3 C₁₋₄ branched or unbranched alkyl, C₁₋₄alkoxy, cyano, di-(C₁₋₃ alkyl)amino, C₁₋₆ alkyl-S(O)_m or halogen;

wherein said cyclic group is optionally attached to a C₁₋₄ saturated or unsaturated branched or unbranched carbon chain wherein said carbon chain is in turn covalently attached to Q, said carbon chain is optionally partially or fully halogenated and wherein one or more methylene groups are optionally replaced by O, N or S(O)_m, wherein said methylene groups are further optionally independently substituted with

1-2 oxo groups and one or more C₁₋₄ branched or unbranched alkyl optionally substituted by one or more halogen atoms;

R₁ is C₃₋₄alkyl branched or unbranched, cyclopropyl or cyclohexanyl
 5 optionally partially or fully halogenated and optionally substituted with one to three C₁₋₃ alkyl groups;

R₃ is selected from the group consisting of
 phenyl, pyridinyl each being optionally substituted with one to five groups
 selected from the group consisting of a C₁₋₆ branched or unbranched alkyl, phenyl,
 10 naphthyl, pyridinyl, C₁₋₆ branched or unbranched alkyl, cyclopropyl, cyclobutyl,
 cyclopentanyl, cyclohexanyl, cycloheptanyl, bicyclopentanyl, bicyclohexanyl,
 bicycloheptanyl, phenyl C₁₋₅ alkyl, naphthyl C₁₋₅ alkyl, halo, cyano, C₁₋₃ alkyloxy
 which may optionally be partially or fully halogenated, phenyloxy, naphthyloxy,
 pyridinyloxy, nitro, di-(C₁₋₃)alkylamino, di-(C₁₋₃)alkyl aminocarbonyl, C₁₋₅ alkyl-
 15 C(O)-C₁₋₄ alkyl, di-(C₁₋₃)alkylamino-C₁₋₅ alkyl, di-(C₁₋₃)alkylamino-S(O)₂, R₄-C₁₋₅
 alkyl, R₅-C₁₋₅ alkoxy, R₆-C(O)-C₁₋₅ alkyl and R₇-C₁₋₅ alkyl-N(R₈)-

5. The process according to claim 4 wherein
 20

L is:

O-CH₂-, O-CH₂CH₂-, O-CH₂CH₂CH₂-, O-CH₂CH₂(CH₃), O-CH₂(CH₃)CH₂-,
 S(O)_mCH₂-, S(O)_mCH₂CH₂-, S(O)_mCH₂CH₂CH₂-, CH₂-, CH₂CH₂-, CH₂CH₂CH₂-, O-
 CH₂C(O)-,

25 HC≡C-CH₂- or HC≡C-CH₂O-;

and Q is *N*-morpholino.

6. The process according to claim 5 wherein L is O-CH₂CH₂-.
 30

7. The process according to claim 6 wherein:

in step 1):

- the suitable base is selected from triethylamine, diisopropylethylamine, N-methylpyrrolidine, DBU, DMAP, N-methylmorpholine, pyridine and methyl pyridine;
- the polar non-protic organic solvent selected from NMP, acetonitrile, DMF, DMAC and DMSO;
- the temperature is about 80°C;
- the reaction time is 4-10 hours;
- R_b is 2,2,2-trichloroethyl;

in step 2):

- Y-R₃ is present in about a two-fold molar excess, wherein Y is B(OH)₂;
- the suitable base is triethylamine or pyridine and is present in about a two-fold molar excess;
- the suitable catalyst is Cu(OAc)₂, (Cu(OH).TMEDA)₂Cl₂ or CuCO₃.Cu(OH)₂ and present at about a 1.5 molar excess;
- the suitable solvent is selected from methylene chloride, 1,4-dioxane, N-methylpyrrolidinone, THF and DMF.

8. The process according to claim 7 wherein:

in step 1):

- suitable base is diisopropylethylamine;
- polar non-protic organic solvent is DMSO;

in step 2):

- the suitable base is pyridine;
- the suitable catalyst is Cu(OAc)₂;
- suitable solvent is methylene chloride.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/02982

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	P. Y. S. LAM ET AL.: "New Aryl/Heteroaryl C-N Bond Cross-coupling Reactions via Arylboronic Acid/Cupric Acetate Arylation" TETRAHEDRON LETTERS, vol. 39, no. 19, 1998, pages 2941-2944, XP002202793 table 1	1-8
A	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. RIN 1529254 XP002202794 abstract & M. R. PAVIA ET AL.: J. MED. CHEM., vol. 33, no. 2, 1990, pages 854-861, -/--	1-8

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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- * & * document member of the same patent family

Date of the actual completion of the international search

20 June 2002

Date of mailing of the international search report

05/07/2002

Name and mailing address of the ISA

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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